| Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables | | | | |
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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Matalon, 2007  Country:  Russia, Ukraine, US, Italy, Brazil, Denmark  Enrollment period:  NR  Funding:  Genetics Research Trust, the Mid-Atlantic Connection for PKU and Allied Disorders (MACPAD), the South Texas Association for PKU and Allied Disorders (STAPAD), and PKU and Allied Disorders of Wisconsin (PADOW), PreKUNil and NeoPhe by PreKU lab, Denmark  Author industry relationship disclosures: None  Design:  RCT | **Intervention:**  Double-blind placebo controlled crossover trial of tabletsof Large neutral Amino Acid (LNAA-NeoPhe) & placebo, with a random order of placebo & LNAA  **Groups:** **G1:** LNAA / placebo **G2:** Placebo /LNAA  **Dosage**: **G1:** 0.5 g/kg/day in 3 divided doses to be taken with meals, which is about one tablet/ kg/day.  **G2:** same as G1 & contained lactose monohydrate, microcrystalline cellulose and colloidal hydrated silica.  1 week washout period prior to the next week of crossover trial  Diet was continued as before the trial  **Assessments:** Blood Phe determined at the beginning & then twice weekly  **Length of follow-up:**  A week after treatment  **Groups, N at enrollment:**  **G1/G2:** 20  N at follow-up:  **G1/G2:** 20 | Inclusion criteria: Should have PKU and old enough to swallow pills  Exclusion criteria:  See inclusion criteria  Age:  G1/G2: range (11-32 years)  Other characteristics, n:  Disease classification: Classical PKU, 19 | **Cognitive:**  **IQ:**  NR  **Phe level, mean:**  **G1/G2:** 932.9 µmol/L  Those adhered to PKU formula (n=7): 531.6 µmol /L  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level, mean ± SD:** (µmol/L)  **G1:** 568.4 (average decline of 364.5 ± 232.),39% reduction (*P* < 0.0001)  **G1 and adhered to formula:** 281.5 (average decline of 250.1 ± 173.7), 47% reduction (*P* = 0.009)  **G2**: 882.66 (decline of 5.4%) (*P* = 0.07)  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  NR  **Modifiers:**  NR |

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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author: Schindeler, 2007  Country:  Australia  Enrollment period:  NR  Funding:  SHS International  Author industry relationship disclosures:  NR  Design:  RCT  Schindeler, 2007 (continued)  Schindeler, 2007 (continued)  Schindeler, 2007 (continued) | **Intervention:**  Double-blind, randomized crossover study with LNAA  Dosage: 250mg/kg/day of LNAA, 3 equal daily doses 4 phases of study:  **G1A:** Phase 1: Usual Medical product, usual Phe restricted diet & LNAA tablets  **G1B:** Phase 2: Usual Medical product, usual Phe restricted diet & placebo tablets  **G1C:** Phase 3: No Medical product, took usual Phe restricted diet & energy intake, LNAA tablets  **G1D:** Phase 4: No Medical product, took usual Phe restricted diet & energy intake, Placebo tablets  Duration: Each phase for 14 days with a 4 week washout period between phases  **Assessments:**  Brain Phe by MRS  Plasma Phe at the completion of each phase  3 day food diary to assess intake of dietary protein  Intelligence by WASI  Components of attention & executive function by CPT-II, CANTAB, D-KEFS  Self-report of mood ratings by DASS  Length of follow-up: end of each phase  All on diet & medical products for PKU  At the end of each phase: median (min,max), Phe intake mg/kg/day G1A: 18.6 (5.3, 27.9)  G1B: 18.5 (6.4, 43.9) G1C: 17.5 (4.5, 29.7) G1D: 21.8 (6.2, 27.9)  Protein total g/kg/day G1A: 1.62 (0.96, 2.10) G1B: 1.43 (0.88, 1.85) G1C: 0.63 (0.34,0.93) G1D: 0.51 (0.17,0.62)  LNAA total g/kg/day G1A: 0.90 (0.53, 1.27) G1B: 0.75 (0.32, 1.05) G1C: 0.35 (0.24,0.46) G1D: 0.15 (0.05,0.21)  Compliance on LNAA supplement - good  **Groups, N at enrollment:**  **Total:** 16  N at follow-up:  **Total:** 16 | Inclusion criteria:  Early treated Classical PKU (plasma Phe at some stage >1000 µmol/L)  Currently on diet & medical products for PKU  Exclusion criteria: see inclusion  Age, median/yrs:  24y 9 m, range (11y 8m to 45y 1m)  Other characteristics, n (%): Classical PKU subjects=16 (100) | **Cognitive:**  **IQ: mean (SD)**  101 (16)  **Phe level:** Previous year Median blood Phe levels used as baseline  Excellent control (<450 µmol/L), n=0  Good control (450-750 µmol/L), n=9  Marginal control (750-1000 µmol/L), n=6  Poor control (>1000 µmol/L), n=1  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  G1C vs. G1D:  Better performance on measures of verbal generativity (*t*=2.657,  *P =* 0.018) and non verbal cognitive flexibility (*t=*2.66, *P* = .018)  G1C vs. G1A:  Better verbal self monitoring (*t=*2.179, *p=*0.046)  G1A & G1B vs. G1C & G1D:  better performances on  attention measures (*F=*23.64, *p=*0.000)  **Phe level:**  Brain Phe, µmol/L, range:  176-365 (no significant differences between phases)  Plasma Phe µmol/L, at the end of each phase, median (min,max):  G1A: 639 (149, 1044)  G1B: 734 (19, 1231)  G1C:958 (553, 1500)  G1D: 1180 (641, 1744)  Significant differences in plasma Phe  between G1C & G1D (p=0.001), between G1A & and G1C  (*P* = 0.001), between G1A & G1D (*P* < 0.0005), between  G1B and G1D (p=0.001), and between G1B and G1C (p=0.023). There was no significant difference between  G1A and G1B (p=0.22), however, plasma Phe was reduced  in most subjects (9 of 16) by an average of 24.9% during G1A  **Plasma Phe/Tyr ratio:** median (min,max) ;  G1A: 10 (1.2, 17.9)  G1B:14 (0.2, 27.5) G1C:18 (8.6, 36.6) G1D: 30 (11.9, 52.1)  **Plasma Phe/Tyr ratio:**  significant differences between G1A  and G1B (*p=*0.017), between phase G1C and G1D (*p=*0.001), between  G1A and G1C (*p=*0.02), between G1A and G1D (*p*<0.001),and between G1B and G1D (*p*<0.001)  No significant diff between G1B & G1C (p=.23)  **Nutritional:**  G1A:NR  G1B:NR G1C: NR G1D: NR  **Quality of Life:**  G1A:NR  G1B:NR G1C: NR G1D: NR  **Harms:** Higher levels of anxiety symptoms while on LNAA (F=5.2, p=.039), G1A & G1C compared to G1B & G1D  **Modifiers:** No correlation between Plasma & brain Phe when Plasma Phe <1200 µmol/L  G1D: Significant correlation between plasma & brain phe (r=0.90, p=.04, where phe ≥1200 µmol/L n=5)  No significant correlations  Between plasma Phe or Phe/Tyr ratio  with total dietary LNAA intake, or dietary Phe  intake  G1A: significant  negative correlations were obtained between plasma  Phe and semantic verbal Fluency (VF-Category;  r=- 0.525, p*=*0.018.  G1B: plasma Phe and inattention  Negatively correlated (CPT-Errors, r = - 0.441, *p=*.044).  G1C: a negative correlation between spatial  working memory and plasma Phe (SWM,  r= - 0.464, *p=*0.035).  G1D: no significant correlations  **Across phases,**  Statistically significant  negative correlations between plasma Phe  and verbal generativity (VF-Letters;  r= - 0.465, (*p=*0.035)  and non-verbal self monitoring (DF-reps,  r = -0.488,  *p=*0.027). |

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| Author:  Matalon, 2006  Country:  US, Ukraine, Russia  Enrollment period:  NR  Funding:  Genetics Research Trust  Author industry relationship disclosures: None  Design:  Uncontrolled open label trial | **Intervention:**  Open-label study of LNAAs (NeoPhe)  **Groups :** **G1:** 0.5g/kg/day of NeoPhe **G2:** 1.0 g/kg/day of NeoPhe  Duration: 1 week  Formulation: NeoPhe divided into 3 doses and taken before meals  Instructed to continue with their diet as before the trial  **Assessments:**  Blood Phe at baseline, 1 wk and 1 week after Rx  **Length of follow-up:**  1 week after the end of Rx  **Groups, N at enrollment:**  **G1:** 8  **G2:** 3  N at follow-up:  **G1:** 8  **G2:** 3 | Inclusion criteria:   * Should have PKU * Old enough to swallow pills   Exclusion criteria:  See inclusion criteria  Age, mean/yrs :  G1: 20.5  G2: 16.5  **Other characteristics:**  **G1+G2:**  All 11 patients were classical PKU  2 responded to BH4 loading, none were on BH4 during study | **Cognitive:**  **IQ:**  NR  **Phe level, mean**  **µmol/L:**  **G1:** 957.4  **G2:** 1,230  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level, mean µmol/L ± SD:**  **G1:** 458.4  **G2:** 549  Drop in Phe, mean ± SD: 601 + 370, n=11, (P = 0.0003)  **% decline in Phe:**  **G1:** 52  **G2:** 55  **G1/BL:** *P* = .004  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  NR  **Modifiers:**  NR |